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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/620,317 | 07/15/2003 | Yunping Li | BBRI-2008US01 | 7947 |

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| EXAMINER | |
|---|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/620,317 | LI ET AL. | |
| | Examiner | Art Unit | |
| | Phyllis G. Spivack | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-12-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' Response filed March 3, 2005 to the Election of Species Requirement is acknowledged. Applicants have elected the compound U0126 as a compound that inhibits kinase activity to delay preterm uterine contractions; calmidazolium as a compound that inhibits the binding of calmodulin to caldesmon to delay preterm uterine contractions; a phorbol ester as a compound that activates the binding of calmodulin to caldesmon for inducing uterine contractions; and okadaic acid as a compound that inhibits a phosphatase enzyme for inducing uterine contractions. Applicants state both a compound that activates a phosphatase enzyme to delay preterm uterine contractions and a compound that activates kinase activity for inducing uterine contractions are unknown.

Claims 1-35 are presented. The subject matter initially under consideration are those methods of delaying preterm uterine contractions wherein U0126 is administered along with those methods for inducing uterine contractions comprising administering calmidazolium, a phorbol ester or okadaic acid. Those methods comprising administering other agents are presently withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as directed to non-elected inventions. Re-affirmation of the elected species is requested when Applicants respond to this Office Action.

An Information Disclosure Statement filed December 12, 2003 is further acknowledged and has been reviewed.

Claims 12-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. The claims are directed to methods of delaying preterm uterine contractions and methods for inducing uterine contractions. The specification provides support for delaying preterm uterine contractions comprising administering U0126.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to both inducing uterine contractions in a pregnant mammal and delaying preterm uterine contractions in a pregnant mammal wherein

either the inhibition or activation of kinase activity is respectively involved (claims 1-11, 16-28 and 33-35). Further, in claims 13-15 and 30-32 the activation and inhibition of a phosphatase enzyme, respectively, are involved in the methods of delaying or inducing uterine contractions.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in obstetrics.

Each condition or factor associated with inducing or delaying uterine contractions disease or disorder has its own specific characteristics and etiology. The art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of various mitogen-activated protein kinase enzyme systems. The claims are also directed to the administration of a compound that affects activation or inhibition of the binding of calmodulin to caldesmon and the administration of a compound that results in decreased levels of caldesmon phosphorylated at a C-terminal serine residue, for which no support is provided in the specification.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the sole administration of U0126 to delay the onset of parturition. The specification is silent with respect to the administration of any other agent, including compounds claimed to be effective in inducing uterine

contractions. Further, Applicants state in the Response to the Request for an Election of species compounds that activate a phosphatase enzyme to delay preterm uterine contractions and compounds that activate kinase activity for inducing uterine contractions, relating to instant claims 13-15, 20-28 and 22-35, are unknown. This is an admission of non-enablement.

The quantity of experimentation necessary

Applicants have failed to provide guidance in the selection of any compounds to induce uterine contractions in a pregnant mammal through a mechanism of action such as activation of a kinase or activation of the binding of calmodulin to caldesmon. In view of the specificity of the kinase or phosphatase enzyme systems allegedly associated with delaying or inducing uterine contractions, the skilled artisan in obstetrics would expect the administration of a particular compound to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding nor any criteria for extrapolating beyond the administration of U0126 for delaying preterm uterine contractions. No clear direction is provided to delay uterine contractions. Absent reasonable *a priori* expectations of success for using a particular compound other than U0126, one skilled in the obstetrics art would have to test extensively many compounds to discover which would inhibit or activate the binding of calmodulin to caldesmon and which would induce uterine contractions. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested,

undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30 is rejected under 35 U.S.C. 102(b) as being anticipated by Arteche et al., Journal of Pharmacology and Experimental Therapeutics.

Arteche teaches the contractile effect of okadaic acid in the rat uterus. The mechanism of action is specifically through inhibition of protein phosphatases type 1 and /or 2A and is related to a direct interaction with the contractile machinery.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-12 and 16-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al., Anesthesiology.

Li teaches the administration of U0126, an MEK activation inhibitor, on RU-486-induced preterm labor in a rat model. The kinase activity inhibited is the kinase activity of ERK. U0126 is a specific inhibitor of mitogen-activated protein kinase kinase.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adamson et al., American Journal of Obstetrics and Gynecology, in view of Balboa et al., Journal of Biological Chemistry.

Adamson teaches the administration of a phorbol ester, phorbol 12-myristate 13-acetate, a known stimulant of prostaglandin production. Balboa teaches the role of prostaglandin production in the initiation of labor in humans. Phorbol 12-myristate 13-acetate is disclosed to be an inducer of free arachidonic acid, the metabolic precursor of prostaglandins, through activation of a protein kinase. Therefore, in view of the teachings of Adamson and Balboa, one skilled in the obstetrics art would have been motivated to administer the phorbol ester, phorbol 12-myristate 13-acetate, to induce uterine contractions in a pregnant mammal. Such would have been obvious in the absence of evidence to the contrary because phorbol 12-myristate 13-acetate is an inducer of free arachidonic acid, the metabolic precursor of prostaglandins. Prostaglandins are required in the initiation of labor.

No claim is allowed.

Manolagas et al., US Patent 6,416,737, is cited to show further the state of the art with respect to the status of U0126 as a specific inhibitor of mitogen-activated protein kinase kinase.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-

0585. The Examiner can normally be reached Mondays to Fridays from 10:30 AM to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Chris Low, can be reached at telephone number 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

PHYLLIS SPIVACK
PRIMARY EXAMINER

May 15, 2005